Positron emission tomography of cerebral dopamine receptors

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CHAPTER 4*

Synthesis and *in vivo* distribution in the rat of several fluorine-18 labeled 5-hydroxy-2-aminotetralin derivatives

In this chapter a method is described for the rapid production, purification and evaluation of 2-[N-n-3-fluoropropyl-N-(4-methylphenyl)ethylamino]-5-hydroxytetralin, 2-[N-n-3-fluoropropyl-N-(4-fluorophenyl)ethylamino]-5-hydroxytetralin and their isotopic fluorine-18 derivatives.

4.1 Introduction

Early reports on the potential dopaminergic activity of related aminotetralin derivatives were published by Cannon,[132] and Woodruff.[133] From the 5-hydroxy-2-aminotetralin series, the analog 2-(*N*-propyl-*N*-phenylethyl-amino)-5-hydroxytetralin (N-0434) and 2-(*N*-propyl-*N*-thienylethylamino)-5-hydroxytetralin (N-0437) were developed, both potent and selective D_2 agonists (Figure 4.1).[134] The high affinity of N-0437 for D_2 receptors was demonstrated *in vitro*, by Beaulieu,[135] and confirmed by Horn and coworkers.[136-139] Although predominantly active in the central nervous system, N-0437 may also suppress peripheral sympathetic nerve function via D_2^{high} receptors.[140,141]

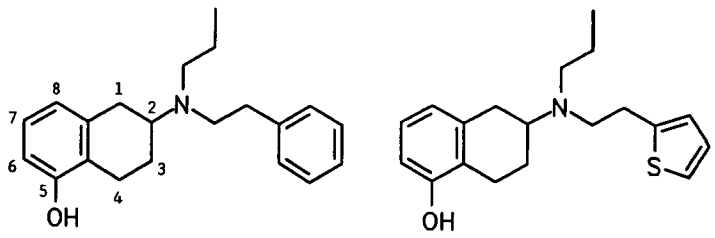

Figure 4.1 Structural formulea of N-0434 and N-0437.

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In this chapter, we describe the production of 2-[*N*-n-3-[^{18}F]-fluoropropyl-*N*-(4-methyl-phenyl)ethylamino]-5-hydroxytetralin, and 2-[*N*-n-3-[^{18}F]-fluoropropyl-*N*-(4-fluoro-phenyl)ethylamino]-5-hydroxytetralin. The fluorine-18 label was introduced via *N*-fluoroalkylation with n.c.a. $^{18}FCH_2CH_2CH_2I$. Although the *N*-fluoroalkylation reaction was successful under thermal heating conditions (refluxing in an oil bath), the labeling was even more successful via microwave exposure as described in Chapter 3. For identification of the labeled compounds, the non-radioactive derivatives (**12**) and (**13**) were synthesized (Scheme 4.1) and were identified via ^{1}H-NMR, ^{13}C-NMR, ^{19}F-NMR and mass spectra, respectively. The distribution of the radioactivity is determined in the brain and peripheral tissues after systemic administration to rats, in order to trace the sites of accumulation and subsequent metabolism of these fluorine-18 labeled derivatives.

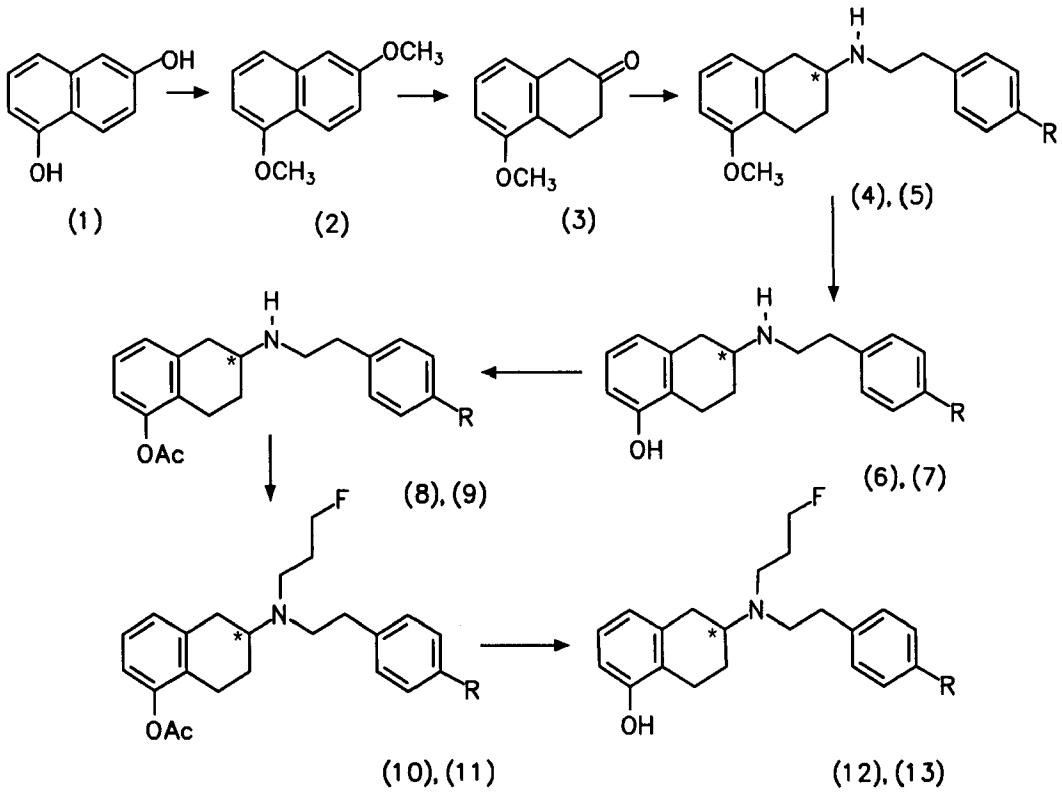
4.2 Chemistry

After methylation of 1,6-dihydroxynaphthalene (**1**) with dimethylsulfate under basic conditions (NaOH), giving a 74% yield, 1,6-dimethoxynaphthalene (**2**) was converted into 5-methoxy-2-tetralon (**3**) via a Birch reduction (yield 65%). The Birch reduction was carried out with sodium and subsequent hydrolysis with HCl yielded the desired product (**3**). The 2-[*N*-alkylamino]-5-methoxytetralin derivatives (**4**) and (**5**) were obtained, giving yields of 60% and 65%, respectively, by aminoalkylation of 5-methoxy-2-tetralon (**3**) followed by reduction under hydrogen atmosphere (Parr apparatus), using PtO_2 as a catalyst. The derivatives (**4**) and (**5**) were demethylated with BBr_3 at room temperature, giving (**6**) and (**7**) in 70% yield. After acylation of the phenolic group with acetylbromide under acid conditions (trifluoroacetic acid), giving (**8**) and (**9**) in 60% yields, the derivatives were *N*-alkylated with 3-fluoropropylbromide under basic conditions ($NaHCO_3$) resulting in the (**10**) and (**11**) in 70% and 75% yield, respectively. The deacylated derivatives (**12**) and (**13**) were obtained by stirring at room temperature in methanol and ethereal hydrochloride (90% yield).

4.3 Experimental part

Acetonitrile used for substitution reactions was stored on molecular sieves 3 Å. HPLC was performed on a Chrompack microporasil column (25 x 7.8 mm I.D.) equipped with an U.V. absorption detector (280 nm) and a NaI radioactivity detector. For purification of the fluorine-18 labeled tetralins, the column was eluted with chloroform (3 ml/min). Radiochemical purity was determined by TLC (Merck DC-alufolien Kieselgel 60, CH_2Cl_2/MeOH 95/5). ^{1}H-NMR, ^{13}C-NMR,

and ^{19}F-NMR were recorded on a Varian VXR-300 spectrophotometer in $CDCl_3$ unless otherwise stated. ^{1}H and ^{13}C chemical shifts were reported in δ units (ppm) relative to the solvents used ($CDCl_3$, 7.26 and 76.9, respectively; CD_3OD, 3.31 and 49.0, respectively). ^{19}F chemical shifts are reported in δ units (ppm) relative to $CFCl_3$ (0.0) as external standard. Exact mass determinations were carried out on a AFJ MS-902 mass spectrometer.



	compound
R = CH_3	(4) (6) (8) (10) (12)
R = F	(5) (7) (9) (11) (13)

***Scheme 4.1** Synthesis of the N-fluoropropyltetralins studied in this chapter.*

The Miele M 686 microwave operations

The Miele M 686 microwave operation procedures and safety precautions were followed as described in the experimental section of Chapter 3.

1,6 dimethoxynaphthalene (2)

To a solution of 1,6-dihydroxynaphthalene ((**1**), 50 g, 0.31 mol) in NaOH (2N, 200 ml) was added $(CH_3)_2SO_4$ (62.5 ml). After 1 hour the solution was cooled to room temperature. To this mixture, NaOH (2N, 142 ml) and $(CH_3)_2SO_4$ (34 ml) were added. After 1.5 hour the solution was heated in an oil bath (1 hour, 100 °C). After cooling to room temperature, the reaction mixture was extracted with CH_2Cl_2 (4x 50 ml). After drying ($MgSO_4$), the organic layer was evaporated under reduced pressure to give an oil. The oil was subjected to flash chromatography (neutral alumina, CH_2Cl_2), yielding (**2**) in 43.7 g (74%), as green crystals, m.p. 50 °C. ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.55 (s, OCH_3), 3.65 (s, OCH_3), 6.30-6.50 (m, 1ArH), 6.90-7.15 (m, 4ArH), 8.10 (d, 1ArH, J= 9 Hz).

5-methoxy-2-tetralon (3)

A solution of 1,6 dimethoxynaphthalene ((**2**), 43 g, 0.23 mol) in absolute EtOH (360 ml) was heated in an oil bath (110 °C) under nitrogen. To this refluxing mixture small pieces of sodium (37 g, 1.2 mol) were added. The mixture was cooled to room temperature, H_2O (170 ml) and HCl (36%, 196 ml) were added. The solution was refluxed for another 0.5 hour. After cooling to room temperature the newly formed NaCl was dissolved by adding H_2O (200 ml). This mixture was extracted with ether (4x 50 ml). The organic layer was washed with water (2x 100 ml) and a saturated NaCl solution (2x 100 ml). After drying ($MgSO_4$), the organic layer was evaporated under reduced pressure. The product was distilled off under vacuo (P= 0.003 torr, T= 125 °C), yielding 26 g (65%) pure (**3**) as a green oil. ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.35 (t, 2H, J= 7 Hz), 3.00 (t, 2H, J= 8 Hz), 3.45 (s, 2H), 3.75 (s, OCH_3), 6.50-7.25 (m, 3ArH).

2-[N-(4-methylphenyl)ethylamino]-5-methoxytetralin (4)

A mixture of 5-methoxy-2-tetralon ((**3**), 2.95 g, 0.02 mol), 2-(4-methylphenyl)-ethylamine (2.19 g, 0.02 mol), and p-toluenesulfonic acid (20 mg, 0.11 mmol) in toluene (50 ml) was heated in an oil bath (2.5 hours, 120 °C). The formed water was separated from toluene by using a Dean-Stark apparatus. The toluene was evaporated under reduced pressure. The residue was redissolved in dry EtOH (100 ml) and hydrogenated in a Parr apparatus, using PtO_2 (230 mg) as catalyst (16 hours, 4 atm). The catalyst was filtered off and the volatiles were evaporated

in vacuo. The oil was isolated and subjected to flash chromatography (silica gel, CH_2Cl_2/MeOH 97/3). The resulting free amine was converted into the hydrochloride salt by adding ethereal hydrochloride (10 ml), yielding 2.71 g (65%) of (**3**). ^{1}H NMR δ (60 MHz, $CDCl_3$) δ 2.25 (s, CH_3), 2.30-3.60 (m, 11H), 3.70 (s, OCH_3), 6.40-7.20 (m, 3ArH), 7.05 (s, 4ArH), m/e 295.195.

2-[N-(4-fluorophenyl)ethylamino]-5-methoxytetralin (5)

For synthesis and purification of 2-[*N*-(4-fluorophenyl)ethylamino]-5-methoxytetralin (**5**), the same procedure was followed as for 2-[*N*-(4-methylphenyl)-ethylamino]-5-methoxytetralin (**4**). ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.75 (s, NH), 1.20-3.30 (m, 11H), 3.95 (s, OCH_3), 6.55-7.30 (m, 7ArH), m/e 299.169.

2-[N-(4-methylphenyl)ethylamino]-5-hydroxytetralin (6)

A mixture of 2-[*N*-(4-methylphenyl)ethylamino]-5-methoxytetralin ((**4**), 500 mg, 1.7 mmol), and BBr_3 (850 mg, 3.4 mmol) in dichloromethane (10 ml) was stirred at room temperature for 24 hours. To this mixture was added MeOH (2 ml). After evaporating the reaction mixture in vacuo, the residue was redissolved in dichloromethane (50 ml) and washed with water (2x 50 ml). After separating and drying the organic layer ($MgSO_4$), it was evaporated under reduced pressure yielding 340 mg (65%) of (**6**). ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.15 (s, NH), 1.20-3.10 (m, 11H), 2.20 (s, CH_3), 4.60 (s, OH), 6.20-7.20 (m, 7ArH).

2-[N-(4-fluorophenyl)ethylamino]-5-hydroxytetralin (7)

For the synthesis and purification of 2-[*N*-(4-fluorophenyl)ethylamino]-5-hydroxytetralin (**7**), the same procedure was followed as for 2-[*N*-(4-methyl-phenyl)-ethylamino]-5-hydroxytetralin (**6**). ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.60 (s, NH), 1.30-3.30 (m, 11H), 4.40 (s, OH), 6.40-7.30 (m, 7ArH).

2-[N-(4-methylphenyl)ethylamino]-5-acetoxytetralin (8)

Under nitrogen 2-[*N*-(4-methylphenyl)ethylamino]-5-hydroxytetralin ((**6**), 250 mg, 0.86 mmol), acetylbromide (210 mg, 1.6 mmol) in trifluoroacetic acid (20 ml) were heated in an oil bath (2.5 hours, 95 °C). After evaporating the reaction mixture in vacuo, the residue was redissolved in chloroform (50 ml) and washed with aqueous K_2CO_3 (10%, 2x 50 ml). The chloroform layer was separated, dried ($MgSO_4$) and evaporated under reduced pressure. The oil was isolated and subjected to flash chromatography (silica gel, CH_2Cl_2/MeOH 95/5), yielding 170 mg (60%) (**8**). ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.40 (s, NH), 2.10-2.20 (s, 2x CH_3), 1.00-3.00 (m, 11H), 6.70-7.20 (m, 7ArH).

2-[N-(4-fluorophenyl)ethylamino]-5-acetoxytetralin (9)

For the synthesis and purification of 2-[*N*-(4-fluorophenyl)ethylamino]-5-acetoxytetralin (**9**), the same procedure was followed as for 2-[*N*-(4-methylphenyl)ethylamino]-5-acetoxytetralin (**8**). ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.30 (s, NH), 2.25 (s, CH_3), 1.00-3.20 (m, 11H), 6.70-7.30 (m, 7ArH).

2-[N-n-3-fluoropropyl-N-(4-methylphenyl)ethylamino]-5-acetoxytetralin (10)

A mixture of 2-[*N*-(4-methylphenyl)ethylamino]-5-acetoxytetralin ((**8**), 160 mg, 0.50 mmol), 3-fluoropropylbromide (105 mg, 0.75 mmol) and $NaHCO_3$ (63 mg, 0.73 mmol) in anhydrous acetonitrile (2 ml) was refluxed in an oil bath (75 hours, 100 °C). After evaporating the solvent under reduced pressure, the residue was subjected to flash chromatography (silica gel, CH_2Cl_2/MeOH 95/5), yielding 110 mg (75%) of (**10**). ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.00-3.10 (m, 15H), 2.30 (s, 2x CH_3), 4.00 (t, H, J= 5.5 Hz), 4.80 (t, H, J= 5.5 Hz), 6.60-7.20 (m, 7ArH). MS m/z (M^+) calc 383.226, obsd 383.224.

2-[N-n-3-fluoropropyl-N-(4-fluorophenyl)ethylamino]-5-acetoxytetralin (11)

For the synthesis and purification of 2-[*N*-n-3-fluoropropyl-*N*-(4-fluorophenyl)-ethylamino]-5-acetoxytetralin (**11**), the same procedure was followed as for 2-[*N*-n-3-fluoropropyl-*N*-(4-methylphenyl)ethylamino]-5-acetoxytetralin (**10**). ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.00-3.10 (m, 11H), 2.20 (s, CH_3), 4.00 (t, H, J= 5.5 Hz), 4.80 (t, H, J= 5.5 Hz), 6.60-7.30 (m, 7ArH). MS m/z (M^+) calc 387.201, obsd 387.200.

2-[N-n-3-fluoropropyl-N-(4-methylphenyl)ethylamino]-5-hydroxytetralin (12)

A solution of 2-[*N*-n-3-fluoropropyl-*N*-(4-methylphenyl)ethylamino]-5-acetoxytetralin ((**10**), 110 mg, 0.28 mmol) and MeOH (20 ml) in Et_2O.HCl (10 ml) was stirred at room temperature for 75 hours. The solvent was evaporated under reduced pressure. The residue was redissolved in dichloromethane (25 ml) and washed with water (2x 25 ml). After drying the organic layer ($MgSO_4$), dichloromethane was evaporated under reduced pressure and the residue was subjected to flash chromatography (silica gel, CH_2Cl_2/MeOH 95/5) yielding 90 mg (94%) of (**12**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, OH), 2.32 (s, CH_3), 1.30-3.00 (m, 15H), 4.41 (t, H, J= 6 Hz), 4.56 (t, H, J= 6 Hz), 6.58-7.25 (m, .7ArH). ^{13}C NMR ($CDCl_3$) δ 20.9 (q), 23.5 (t), 29.57 (t), 32.01 (t), 35.07 (t), 45.78 (t), 52.8 (t), 56.4 (s), 81.12 (t, CH_2F), 83.29 (t, CH_2F), 111.86 (d), 121.5 (d), 122.78 (s), 126.26 (d), 128.49 (d), 128.67 (d), 128.86 (d), 135.3 (s), 137.25 (s), 138.07 (s), 153.3 (s). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ -220 (m, CH_2F). MS m/z (M^+) calc 341.215, obsd 341.213.

2-[N-n-3-fluoropropyl-N-(4-fluorophenyl)ethylamino]-5-hydroxytetralin (13)

For the synthesis and purification of 2-[*N*-n-3-fluoropropyl-*N*-(4-fluorophenyl)-ethylamino]-5-hydroxytetralin (**13**), the same procedure was followed as for 2-[*N*-n-3-fluoropropyl-*N*-(4-methylphenyl)ethylamino]-5-hydroxytetralin (**12**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60-3.00 (m, 15H), 4.39 (t, H, J= 6 Hz), 4.55 (t, H, J= 6 Hz), 6.58-7.16 (m, 7ArH). ^{13}C NMR ($CDCl_3$) δ 23.5 (t), 25.3 (t), 31.95 (t), 34.7 (t), 45.75 (t), 45.8 (t), 52.85 (t), 56.25 (d), 81.03 (t, CH_2F), 83.2 (t, CH_2F), 111.92 (d), 114.91 (d), 115.03 (d), 121.56 (d), 122.78 (s), 126.32 (d), 129.96 (d), 130.08 (d), 136.09 (d), 138.01 (s), 153.3 (s), 159.62 (s), 162.86 (s). ^{19}F-NMR ($CDCl_3$, $CFCl_3$) δ -220 (m, CH_2F), -120 (s, Ar-F). MS m/z (M^+) calc 345.190, obsd 345.187.

Production of [^{18}F]-fluoride

For the production of [^{18}F]-fluoride the same procedure was followed as described in the experimental section of Chapter 3.

3-[^{18}F]-fluoropropyliodide

For the synthesis and purification of 3-[^{18}F]-fluoropropyliodide, the same procedure was followed as described in the experimental section of Chapter 3.

2-[N-n-3-[^{18}F]-fluoropropyl-N-(4-methylphenyl)ethylamino]-5-hydroxytetralin

To the 3-[^{18}F]-fluoropropyliodide solution (1 ml), 2-[*N*-(4-methylphenyl)ethyl-amino]-5-hydroxytetralin (5 mg, 0.018 mmol), NaI (4 mg, 0.025 mmol) and $NaHCO_3$ (2 mg, 0.023 mmol) were added. The reaction glass tube was sealed and transferred in a Miele M 686 microwave oven (600 Watt, 5 times 90 sec). After cooling the reaction mixture to room temperature, the acetonitrile and unreacted 3-[^{18}F]-fluoropropyliodide were evaporated under reduced pressure. The residue was redissolved in $CHCl_3$ and passed through a millipore SR-filter. The product was purified and isolated via HPLC. The fractions containing radioactivity (retention time 8.5 minutes) were pooled and evaporated under reduced pressure. The product was redissolved in EtOH (96%, 0.1 ml). This solution was diluted with saline (2 ml). Before injection, the solution was sterilized by passing it through a membrane filter (Millex-GS, 0.22 μm).

2-[N-n-3-[^{18}F]-fluoropropyl-N-(4-fluorophenyl)ethylamino]-5-hydroxytetralin

For the synthesis of 2-[*N*-n-3-[^{18}F]-fluoropropyl-*N*-(4-fluorophenyl)ethylamino]-5-hydroxytetralin the same procedure was followed as described for the synthesis of 2-[*N*-n-3-[^{18}F]-fluoropropyl-*N*-(4-methylphenyl)ethylamino]-5-hydroxytetralin. For the purification of the product the same column was used (retention time 9 min).

4.4 Animal experiments

Male albino rats (Wistar derived strain weight 180-250 g, bred at the Centraal Proefdieren Laboratorium Groningen, the Netherlands) were used. The sterilized solutions were injected intravenously (tail vein) at doses of 20 MBq per animal, with a specific activity ranging from 9 - 10 GBq/μmol (10 nmol/kg rat). The rats were killed by decapitation at 15, 30 and 60 minutes after injection. The brain and other tissues were rapidly removed and dissected.[142] The radioactivity in the striatum, frontal cortex, cerebellum and a variety of peripheral tissues was measured. To assess the possible competition between endogenous dopamine and specific radiolabeled ligand binding, cerebral dopamine was depleted with reserpine.[143] Reserpine (5 mg/kg rat) was injected i.p. twice: 27 hours and 6 hours before administration of the radiolabeled ligand. The rats, pretreated with reserpine, were killed by decapitation at 30 minutes after the injection of the radiolabeled ligands. Data expressed as mean SEM of 4 animals. Non-parametric statistical tests were used.[144] Independent samples were analyzed with the two sided T-Test.

4.5 Results and discussion

Our aim was to develop a method for a rapid *N*-fluoroalkylation of tetralins, and to evaluate the *in vivo* distribution of the isotopic fluorine-18 labeled derivatives of these tetralins in rats and in particular in the rat brain.

The reductive alkylation of 5-methoxy-2-tetralon (**3**) under hydrogen atmosphere is a synthesis route which established the formation of only *N*-monoalkylated derivatives, such as (**4**) and (**5**). During the reduction under hydrogen atmosphere, a chiral centre at the 2-position is generated. Subsequently (**4**) and (**5**) were *O*-demethylated. *O*-demethylation under acid conditions (HBr, HI or BBr_3) might occur with in situ defluorination of the *N*-fluoro-alkylated derivatives. With this in mind, we decided to acylate the phenolic group of the tetralin unit with acetylbromide. This approach proved to be successful, while under mild acid conditions (ethereal HCl) compound (**12**) and (**13**) could be isolated in good yields. After 75 hours refluxing (oil bath), the fluorine-19 derivatives (**10**) and (**11**) were prepared via *N*-fluoroalkylation with fluoro-propylbromide, in chemical yields of 75%. *N*-fluoroalkylation of the tetralins with fluoropropyliodide was not successful, due to hydrogeniodide elimination from fluoropropyliodide. The formation of fluoropropene was confirmed by ^{1}H-

NMR. However, synthesis of the fluorine-18 labeled derivatives under thermal conditions was even more successful when carried out with [^{18}F]-fluoropropyl-iodide instead off [^{18}F]-fluoropropylbromide (radiochemical yields 3% and 0.3% c.f.d., resp.). The difference between the radioactive and non-radioactive synthesis may be caused by different mechanisms (S_N2 versus pseudo S_N1 reactions). The radiochemical yield could also be improved by application of microwaves instead of heating in an oil bath (Chapter 3). The n.c.a. *N*-[^{18}F]-fluoropropyltetralins were prepared with a decay corrected radiochemical yield of 11%, based on 3-[^{18}F]-fluoropropyliodide. The total preparation time for both derivatives was 115 minutes. The specific activities after HPLC separation ranged from 15-75 GBq/μmol. The radiochemical purities were found to be better than 99% as determined by TLC. Beside *N*-fluoroalkylation of the tetralin precursors, fluoroalkylation of the hydroxyl group at the 5-position can be expected. To deal with this problem, the phenolic group was protected during the non-radioactive synthesis. Since the HPLC separation of the *N*-alkylated and *O*-alkylated tetralin products was satisfactory, the radiolabeling reaction was carried out with unprotected precursors.

For the *in vivo* evaluation of the radioactive compounds, a racemic mixture of products was injected. The mass of the injected dose (10 nmol/kg rat) is assumed to be lower than B_{max} of the D_2 receptor in rat brain.[145] Although only one of the isomers is probably pharmacologically active, the specific/non-specific binding ratio will not be grossly effected by the other isomer.

The radioactivity distribution in brain and other tissues of compound (**12**) and (**13**) is shown in figure 4.2 and figure 4.3, respectively. Examining the peripheral tissues, remarkably high uptakes for both *N*-[^{18}F]-fluoropropyltetralin derivatives were found in the adrenal gland. Even after 60 minutes the radioactive uptake of compound (**13**) in the adrenal gland was still high. The major route of metabolism of N-0437 is glucuronidation at the phenolic group;[146] high accumulation of the metabolite in the adrenal gland is unlikely.

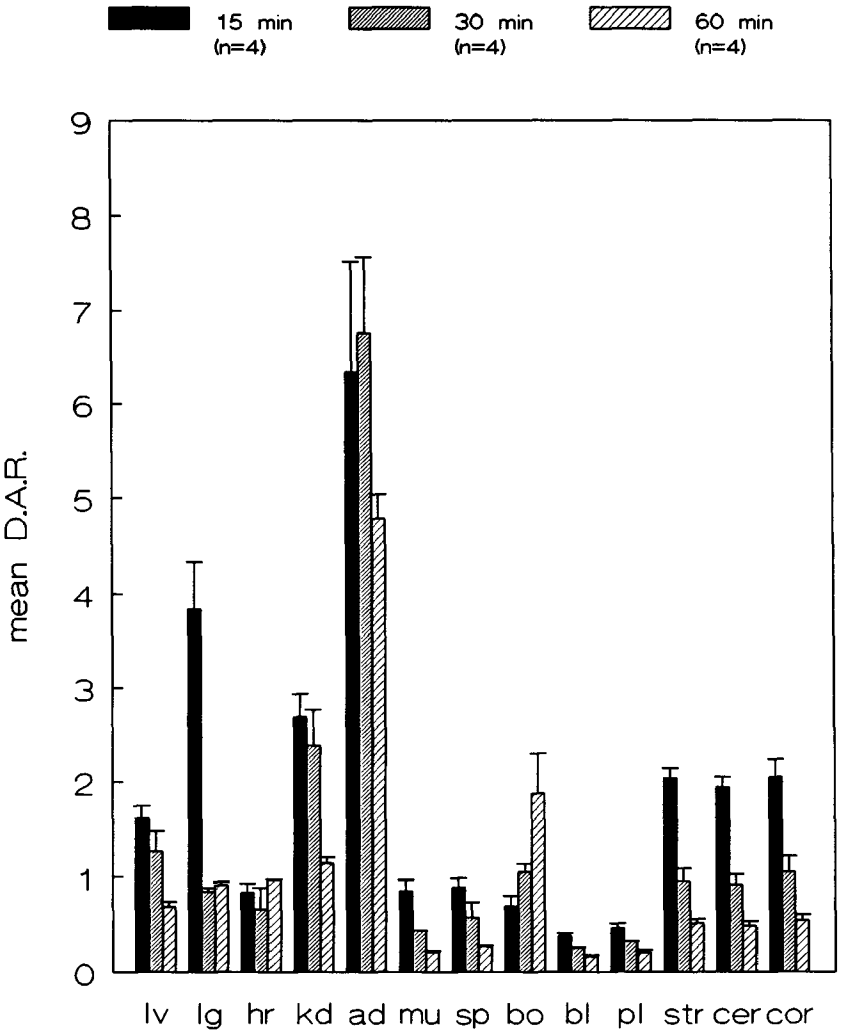


Figure 4.2 *Mean DAR values in peripheral tissues (liver (lv), lungs (lg), heart (hr), kidney (kd), adrenal (ad), muscle (mu), spleen (sp), bone (bo), blood (bl), and plasma (pl)) and in rat brain (striatum (str), cerebellum (cer), and frontal cortex (cor)) at 15, 30, and 60 minutes after administration of 2-[N-n-3-[^{18}F]-fluoropropyl-N-(4-fluorophenyl)-ethylamino]-5-hydroxytetralin (10 nmol/kg) to rats; mean values ± SEM are given, number of rats between parenthesis.*

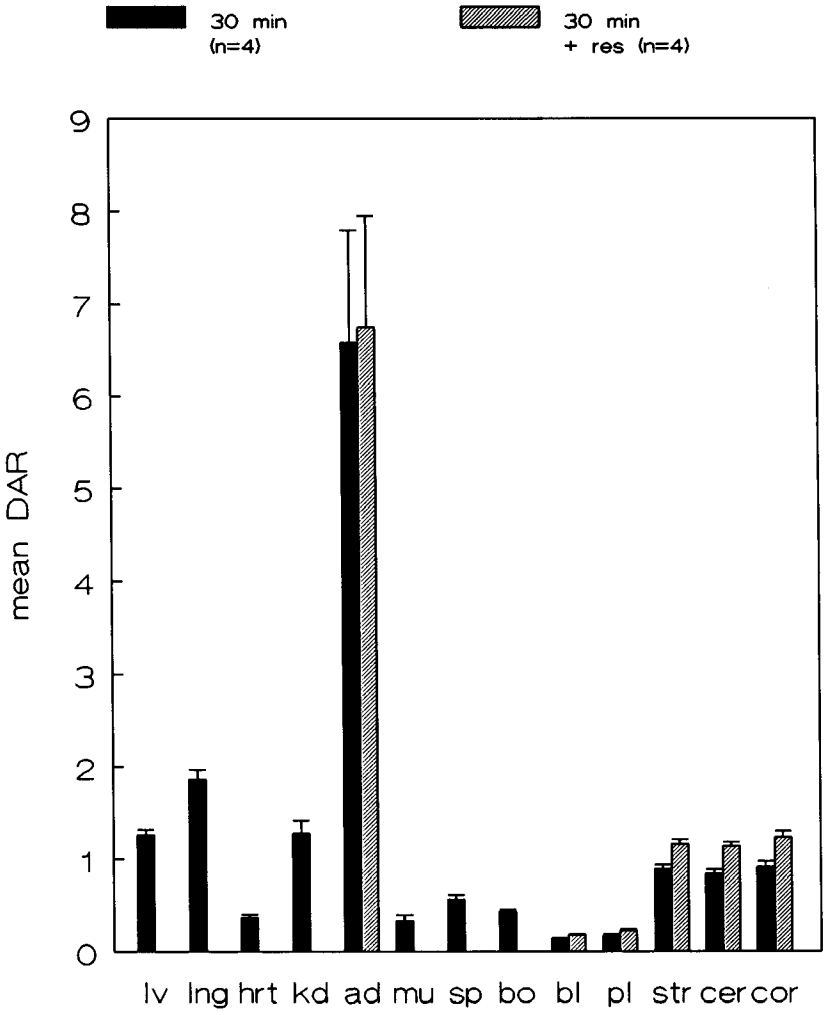


Figure 4.3 *Mean DAR values in peripheral tissues (liver (lv), lungs (lg), heart (hr), kidney (kd), adrenal (ad), muscle (mu), spleen (sp), bone (bo), blood (bl), and plasma (pl)) and in rat brain (striatum (str), cerebellum (cer), and frontal cortex (cor)) at 30 minutes after administration of 2-[N-n-3-[^{18}F]-fluoropropyl-N-(4-methylphenyl)ethylamino]-5-hydroxytetralin (10 nmol/kg) to control rats and to rats pretreated with reserpine; mean values ± SEM are given, number of rats between parenthesis.*

At 15 minutes, the radioactivity in the brain area is much higher than in the plasma, indicating that this labeled compound (**13**) passes the blood-brain barrier very well. Although the optimum partition coefficient (log *P*) for this class of compounds is not known, the lipophilicity of our labeled compounds is probably sufficiently high to pass the blood-brain barrier. The partition coefficients for compounds (**12**) and (**13**) are presented in table 4.1.

compound	**log $P_{30\ min}$**
compound (**12**)	1.50
compound (**13**)	2.08

Table 4.1 *Partition coefficients after 30 minutes in a phosphate buffer at physiological pH (7.4) and temperature (37 °C) for the different tetralin derivatives.*

In table 4.2 the radioactive uptake in rat brain of the fluorine-18 labeled compound (**13**) is presented 15, 30 and 60 minutes after intravenous administration.

tissue	**15 minutes**	**30 minutes**	**60 minutes**
striatum	2.04 ± 0.10	0.96 ± 0.13	0.52 ± 0.04
cerebellum	1.94 ± 0.11	0.92 ± 0.11	0.49 ± 0.05
fr. cortex	2.05 ± 0.19	1.05 ± 0.17	0.55 ± 0.06
NA + TO*	1.97 ± 0.20	0.91 ± 0.19	0.51 ± 0.06

* Nucleus Accumbens and Tuberculum Olfactorius

Table 4.2 *In vivo distribution of 2-[N-n-3-[^{18}F]-fluoropropyl-N-(4-fluoro-phenyl)ethylamino]-5-hydroxytetralin (10 nmol/kg) in rats at 15, 30 and 60 minutes after administration. Mean DAR values with SEM are given. Number of rats for each group: 4.*

At all time points (15, 30 and 60 minutes), the radioactivity levels of compound (**12**) and compound (**13**) at 30 minutes in the striatum, nucleus accumbens and tuberculum olfactorius were not significantly higher than in the cerebellum and frontal cortex. The radioactive uptake of the [^{18}F]-fluoropropyltetralin derivatives in the areas rich in dopamine D_2 receptors, were not affected after dopamine depletion with reserpine (table 4.3).

tissue	compound (12) controls	reserpine	compound (13) controls	reserpine
striatum	0.89 ± 0.04	1.16 ± 0.05	0.96 ± 0.13	1.11 ± 0.17
cerebellum	0.84 ± 0.04	1.14 ± 0.04	0.92 ± 0.11	0.98 ± 0.15
fr. cortex	0.91 ± 0.06	1.23 ± 0.07	1.05 ± 0.17	1.20 ± 0.26
NA + TO	0.90 ± 0.10	1.19 ± 0.07	0.91 ± 0.19	1.25 ± 0.26

* Nucleus Accumbens and Tuberculum Olfactorius

Table 4.3 *In vivo distribution of 2-[N-n-3-[^{18}F]-fluoropropyl-N-(4-fluorophenyl)ethyl-amino]-5-hydroxytetralin (10 nmol/kg) and 2-[N-n-3-[^{18}F]-fluoro-propyl-N-(4-methyl-phenyl)ethylamino]-5-hydroxytetralin (10 nmol/kg) in rats, pretreated with reserpine (1 mg/kg), at 30 minutes after administration. Mean DAR values with SEM are given. Number of rats for each group: 4.*

In conclusion, we have developed a method for a rapid *N*-[^{18}F]-fluoroalkylation of several tetralins. By using microwave exposure, the radiochemical yield of both compounds could be improved. Unfortunately, these compounds did not prove to be effective tracers for the visualization of D_2 dopamine receptors with PET: no significant difference was observed between the accumulation of radioactivity in target/non-target tissue during the *in vivo* experiments in rats. A possible clinical application of these tracers is the *in vivo* visualization of the adrenal glands.